CLAIMS

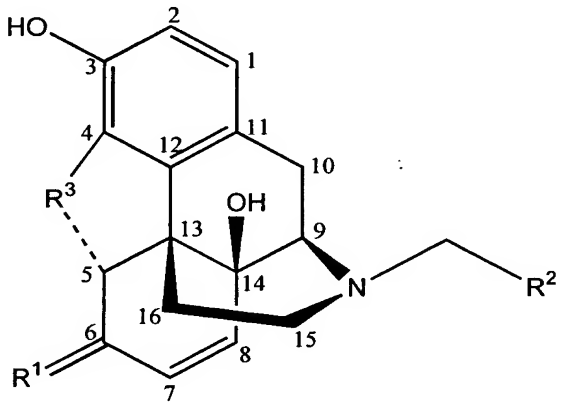
I CLAIM:

1. A method of enhancing efficacy of a non-opioid CNS-active agent comprising: co-administering to a patient a therapeutic dose of the non-opioid CNS-active agent and an amount of an inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain, wherein the drug transporter is an ABC drug transporter.

2. The method of claim 1, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

3. The method of claim 2, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

4. The method of claim 1, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;
wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and
wherein R^3 is O, CH_2 or NH.

5. The method of claim 1, wherein the drug transporter is a P-glycoprotein.

6. The method of claim 5, wherein the P-glycoprotein is PGP1a.

7. The method of claim 1, further comprising administering to the patient an opioid receptor agonist.

8. The method of claim 7, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

9. The method of claim 8, wherein the adverse side effect is constipation.

10. The method of claim 1, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

11. The method of claim ~~1~~, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

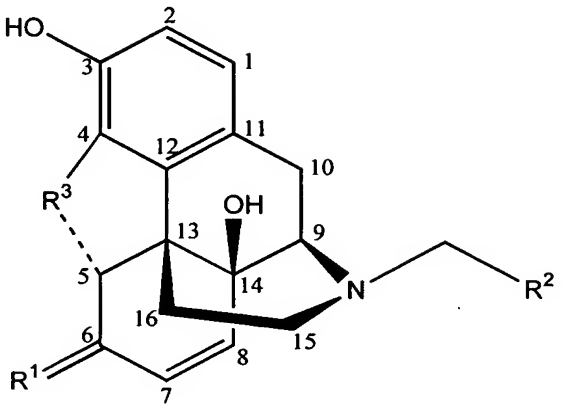
12. A method of enhancing efficacy of a non-opioid CNS-active agent comprising:

co-administering to a patient a sub-therapeutic dose of the non-opioid CNS-active agent and an amount of an inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain, wherein the drug transporter is an ABC drug transporter.

13. The method of claim 12, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

14. The method of claim 13, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

15. The method of claim 12, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

16. The method of claim 12, wherein the drug transporter is a P-glycoprotein.

17. The method of claim 16, wherein the P-glycoprotein is PGP1a.

18. The method of claim 12, further comprising administering to the patient an opioid receptor agonist.

19. The method of claim 18, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

20. The method of claim 19, wherein the adverse side effect is constipation.

21. The method of claim 12, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

22. The method of claim ~~12~~, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

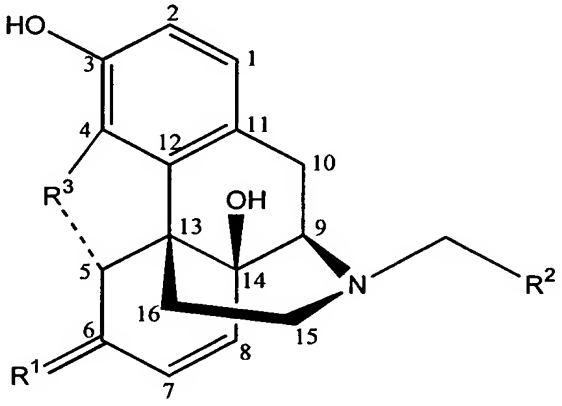
a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;
a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and
a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

23. A method of enhancing efficacy of a non-opioid CNS-active agent comprising:
co-administering to a patient a therapeutic dose of the non-opioid CNS-active agent and an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain, wherein the drug transporter is an ABC drug transporter.

24. The method of claim 23, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

25. The method of claim 24, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

26. The method of claim 23, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;
wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

27. The method of claim 23, wherein the drug transporter is a P-glycoprotein.

28. The method of claim 27, wherein the P-glycoprotein is PGP1a.

29. The method of claim 23, further comprising administering to the patient an opioid receptor agonist.

30. The method of claim 29, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

31. The method of claim 30, wherein the adverse side effect is constipation.

32. The method of claim 23, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

33. The method of claim 23, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

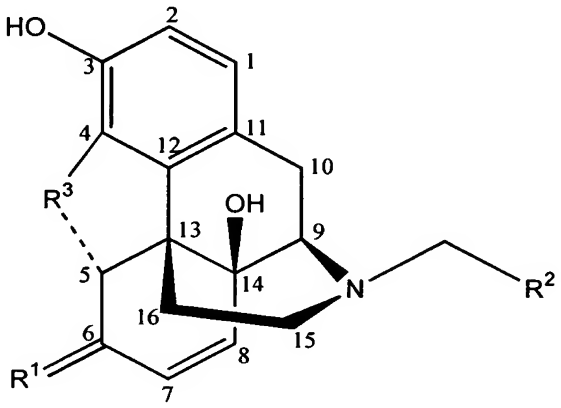
34. A method of enhancing efficacy of a non-opioid CNS-active agent comprising:

co-administering to a patient a sub-therapeutic dose of the non-opioid CNS-active agent and an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain, wherein the drug transporter is an ABC drug transporter.

35. The method of claim 34, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

36. The method of claim 35, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

37. The method of claim 34, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;
wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and
wherein R^3 is O, CH_2 or NH.

38. The method of claim 34, wherein the drug transporter is a P-glycoprotein.

39. The method of claim 38, wherein the P-glycoprotein is PGP1a.

40. The method of claim 34, further comprising administering to the patient an opioid receptor agonist.

41. The method of claim 40, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

42. The method of claim 41, wherein the adverse side effect is constipation.

43. The method of claim 34, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

44. The method of claim 34, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

45. A method of reversing tolerance to a non-opioid CNS-active agent comprising co-administering to a patient who is tolerant to the non-opioid CNS-active agent :

(a) an amount of an inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain, wherein the drug transporter is an ABC drug transporter, and

(b) the non-opioid CNS-active agent to which the patient developed tolerance.

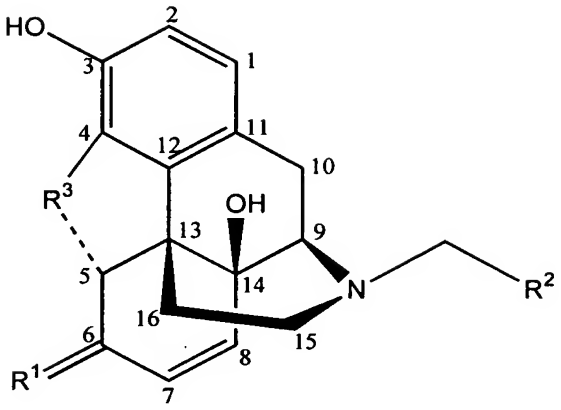
46. The method of claim 45, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

47. The method of claim 46, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

48. The method of claim 45, wherein the drug transporter is a P-glycoprotein.

49. The method of claim 48, wherein the P-glycoprotein is PGP1a.

50. The method of claim 45, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

51. The method of claim 45, further comprising administering to the patient an opioid receptor agonist.

52. The method of claim 51, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

53. The method of claim 52, wherein the adverse side effect is constipation.

54. The method of claim 45, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

55. The method of claim 45, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

56. A method of reversing tolerance to a non-opioid CNS-active agent comprising co-administering to a patient who is tolerant to the non-opioid CNS-active agent:

(a) an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain, wherein the drug transporter is an ABC drug transporter, and

(b) the non-opioid CNS-active agent to which the patient developed tolerance.

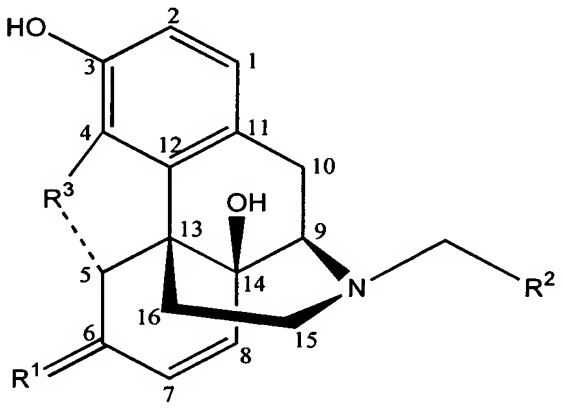
57. The method of claim 56, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

58. The method of claim 57, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

59. The method of claim 56, wherein the drug transporter is a P-glycoprotein.

60. The method of claim 59, wherein the P-glycoprotein is PGP1a.

61. The method of claim 56, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

62. The method of claim 56, further comprising administering to the patient an opioid receptor agonist.

63. The method of claim 62, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

64. The method of claim 63, wherein the adverse side effect is constipation.

65. The method of claim 56, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

66. The method of claim 56, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

67. A method of treating a patient with chronic pain comprising:

repeatedly over a period of time, co-administering to a patient a therapeutic or sub-therapeutic dose of a non-opioid CNS-active agent and an amount of an inhibitor of drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain;

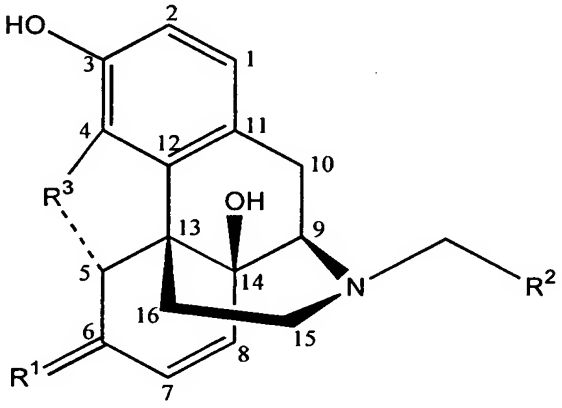
wherein the period of time is greater than the period of time in which the patient would develop tolerance to or develop dependence upon the non-opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter, and wherein the drug transporter is an ABC drug transporter.

68. The method of claim 67, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

69. The method of claim 68, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

70. The method of claim 67, further comprising administering to the patient an opioid receptor agonist.

71. The method of claim 67, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;
wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and
wherein R^3 is O, CH_2 or NH.

72. The method of claim 67, wherein the period of time is greater than the period of time in which the patient would develop tolerance to the non-opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

73. The method of claim 67, wherein the period of time is greater than the period of time in which the patient would develop dependence upon the non-opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

74. The method of claim 67, wherein the drug transporter is a P-glycoprotein.

75. The method of claim 74, wherein the P-glycoprotein is PGP1a.

76. The method of claim 75, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

77. The method of claim 76, wherein the adverse side effect is constipation.

78. The method of claim 67, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

79. The method of claim 67, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

80. A method of treating a patient with chronic pain comprising:

repeatedly over a period of time, co-administering to a patient a therapeutic or sub-therapeutic dose of an non-opioid CNS-active agent and an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain;

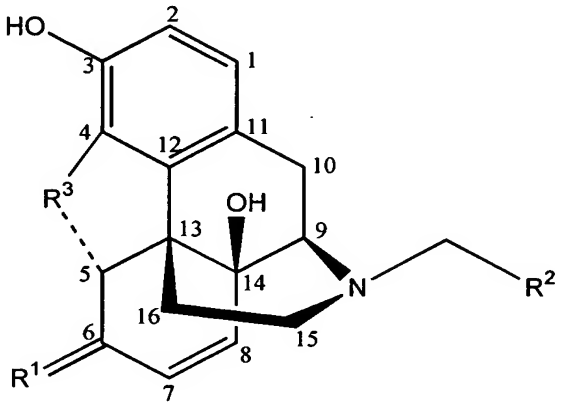
wherein the period of time is greater than the period of time in which the patient would develop tolerance to or develop dependence upon the non-opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter, and wherein the drug transporter is an ABC drug transporter.

81. The method of claim 80, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

82. The method of claim 81, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

83. The method of claim 80, further comprising administering to the patient an opioid receptor agonist.

84. The method of claim 80, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;
wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and
wherein R^3 is O, CH_2 or NH.

85. The method of claim 80, wherein the period of time is greater than the period of time in which the patient would develop tolerance to upon the non-opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

86. The method of claim 80, wherein the period of time is greater than the period of time in which the patient would develop dependence upon the non-opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

87. The method of claim 80, wherein the drug transporter is a P-glycoprotein.

88. The method of claim 87, wherein the P-glycoprotein is PGP1a.

89. The method of claim 88, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

90. The method of claim 89, wherein the adverse side effect is constipation.

91. The method of claim 80, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

92. The method of claim 80, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

93. A method of controlling chronic pain without dependence upon a CNS-active agent comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of a non-opioid CNS-active agent; and

(b) an amount of an inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain,

wherein the co-administration of the inhibitor of the drug transporter with the non-opioid CNS-active agent prevents the patient from developing dependence upon the CNS-active agent, and wherein the drug transporter is an ABC drug transporter.

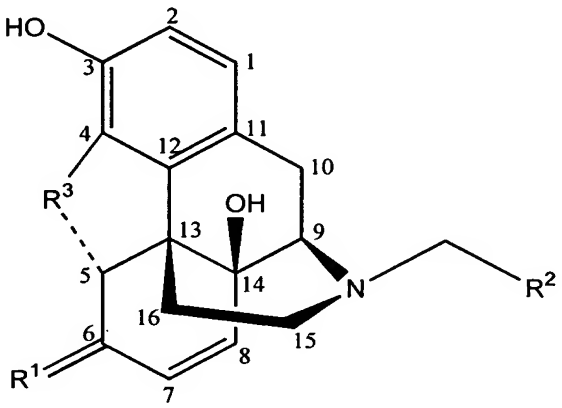
94. The method of claim 93, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

95. The method of claim 94, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

96. The method of claim 93, further comprising administering to the patient an opioid receptor agonist.

97. The method of claim 93, wherein the therapeutic or sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop dependence upon the non-opioid CNS-active agent.

98. The method of claim 93, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;
wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and
wherein R^3 is O, CH_2 or NH.

99. The method of claim 93, wherein the drug transporter is a P-glycoprotein.

100. The method of claim 99, wherein the P-glycoprotein is PGP1a.

101. The method of claim 96, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

102. The method of claim 101, wherein the adverse side effect is constipation.

103. The method of claim 93, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

104. The method of claim ~~93,~~ wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

105. A method of controlling chronic pain without dependence upon a CNS-active agent comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of a non-opioid CNS-active agent; and

(b) an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain,

wherein the co-administration of the inhibitor of the drug transporter with the non-opioid CNS-active agent prevents the patient from developing dependence upon the CNS-active agent, and wherein the drug transporter is an ABC drug transporter.

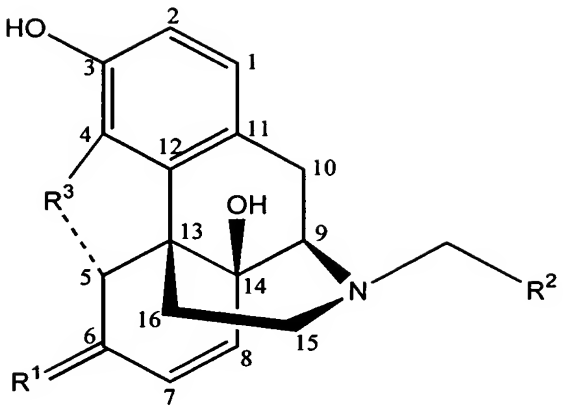
106. The method of claim 105, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

107. The method of claim 106, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

108. The method of claim 105, further comprising administering to the patient an opioid receptor agonist.

109. The method of claim 105, wherein the sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop a drug dependence upon the non-opioid CNS-active agent.

110. The method of claim 105, wherein the inhibitor of the drug transporter is is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

111. The method of claim 105, wherein the drug transporter is a P-glycoprotein.

112. The method of claim 111, wherein the P-glycoprotein is PGP1a.

113. The method of claim 108, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

114. The method of claim 113, wherein the adverse side effect is constipation.

115. The method of claim 105, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

116. The method of claim 105, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

117. A method of controlling chronic pain without tolerance to a CNS-active agent comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of a non-opioid CNS-active agent; and

(b) an amount of an inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain,

wherein the co-administration of the inhibitor of the drug transporter with the non-opioid CNS-active agent prevents the patient from developing tolerance to the CNS-active agent, and wherein the drug transporter is an ABC drug transporter.

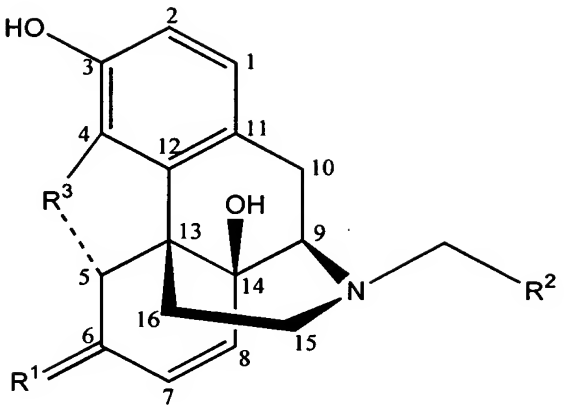
118. The method of claim 117, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

119. The method of claim 118, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

120. The method of claim 117, further comprising administering to the patient an opioid receptor agonist.

121. The method of claim 117, wherein the sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop tolerance to the non-opioid CNS-active agent.

122. The method of claim 117, wherein the inhibitor of the drug transporter is is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

123. The method of claim 117, wherein the drug transporter is a P-glycoprotein.

124. The method of claim 123, wherein the P-glycoprotein is PGP1a.

125. The method of claim 120, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

126. The method of claim 125, wherein the adverse side effect is constipation.

127. The method of claim 117, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

128. The method of claim 117, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

129. A method of controlling chronic pain without tolerance to a CNS-active agent comprising co-administering to a patient :

(a) a sub-therapeutic dose of a non-opioid CNS-active agent; and

(b) an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain,

wherein the co-administration of the inhibitor of the drug transporter with the non-opioid CNS-active agent prevents the patient from developing tolerance to the CNS-active agent, and wherein the drug transporter is an ABC drug transporter.

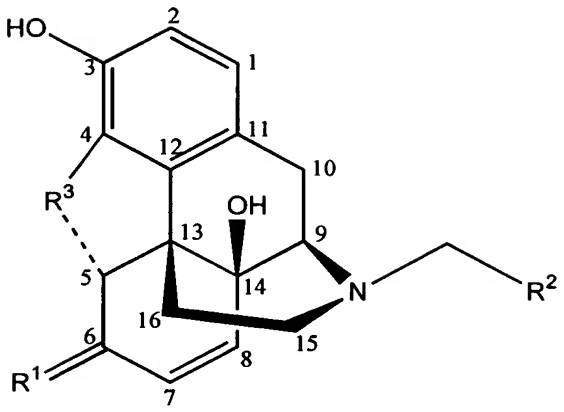
130. The method of claim 129, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

131. The method of claim 130, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

132. The method of claim 129, further comprising administering to the patient an opioid receptor agonist.

133. The method of claim 129, wherein the sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop tolerance to the non-opioid CNS-active agent.

134. The method of claim 129, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

135. The method of claim 129, wherein the drug transporter is a P-glycoprotein.

136. The method of claim 135, wherein the P-glycoprotein is PGP1a.

137. The method of claim 132, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

138. The method of claim 137, wherein the adverse side effect is constipation.

139. The method of claim 129, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

140. The method of claim 129, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

141. A method of controlling chronic pain with a CNS-active agent without developing withdrawal comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of a non-opioid CNS-active agent; and

(b) an amount of an inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain,

wherein the co-administration of the inhibitor of the drug transporter with the non-opioid CNS-active agent prevents the patient from developing withdrawal, and wherein the drug transporter is an ABC drug transporter.

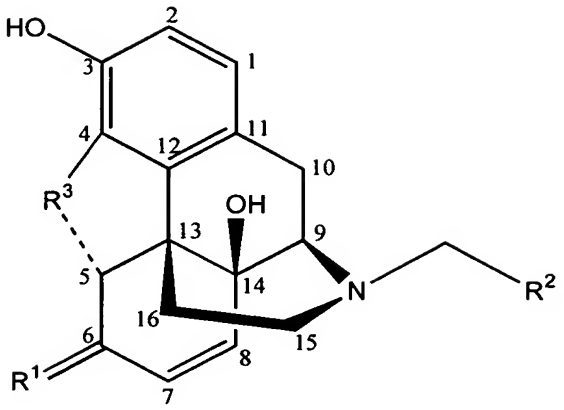
142. The method of claim 141, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

143. The method of claim 142, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

144. The method of claim 141, further comprising administering to the patient an opioid receptor agonist.

145. The method of claim 141, wherein the sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop withdrawal to the non-opioid CNS-active agent.

146. The method of claim 141, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

147. The method of claim 141, wherein the drug transporter is a P-glycoprotein.

148. The method of claim 147, wherein the P-glycoprotein is PGP1a.

149. The method of claim 144, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

150. The method of claim 149, wherein the adverse side effect is constipation.

151. The method of claim 141, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

152. The method of claim 141, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

153. A method of controlling chronic pain with a CNS-active agent without developing withdrawal comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of a non-opioid CNS-active agent; and

(b) an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain,

wherein the co-administration of the inhibitor of the drug transporter with the non-opioid CNS-active agent prevents the patient from developing withdrawal, and wherein the drug transporter is an ABC drug transporter.

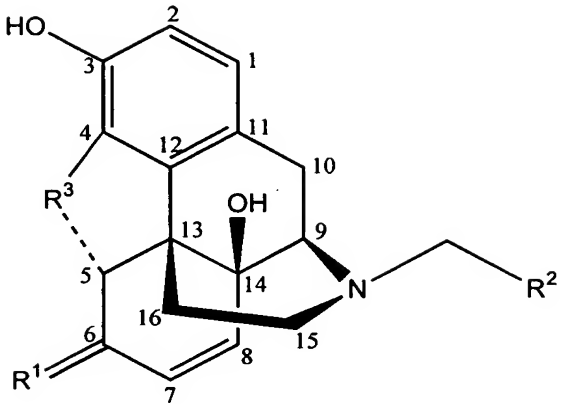
154. The method of claim 153, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

155. The method of claim 154, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

156. The method of claim 153, further comprising administering to the patient an opioid receptor agonist.

157. The method of claim 153, wherein the sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop withdrawal to the non-opioid CNS-active agent.

158. The method of claim 153, wherein the inhibitor of the drug transporter is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

159. The method of claim 153, wherein the drug transporter is a P-glycoprotein.

160. The method of claim 159, wherein the P-glycoprotein is PGP1a.

161. The method of claim 156, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

162. The method of claim 161, wherein the adverse side effect is constipation.

163. The method of claim 153, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

164. The method of claim 153, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

165. A method of preventing a patient from becoming tolerant to or dependent upon a non-opioid CNS-active agent comprising co-administering to the patient:

(a) an amount of an inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain, wherein the drug transporter is an ABC drug transporter; and

(b) a therapeutic or sub-therapeutic dose of non-opioid CNS-active agent, thereby preventing the patient from becoming tolerant to or dependent upon the non-opioid CNS-active agent.

166. The method of claim 165, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

167. The method of claim 166, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

168. The method of claim 165, further comprising administering to the patient an opioid receptor agonist.

169. The method of claim 165, wherein the sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop tolerance or dependence.

170. The method of claim 165, wherein the drug transporter is a P-glycoprotein.

171. The method of claim 170, wherein the P-glycoprotein is PGP1a.

172. The method of claim 168, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

173. The method of claim 172, wherein the adverse side effect is constipation.

174. The method of claim 165, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

175. The method of claim 165, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

176. A method of preventing a patient from becoming tolerant to or dependent upon a non-opioid CNS-active agent comprising co-administering to the patient:

(a) an amount of an inhibitor of a drug transporter effective to increase the concentration of the non-opioid CNS-active agent in the brain, wherein the drug transporter is an ABC drug transporter; and

(b) a therapeutic or sub-therapeutic dose of the non-opioid CNS-active agent, thereby preventing the patient from becoming tolerant to or dependent upon the non-opioid CNS-active agent.

177. The method of claim 176, wherein the inhibitor of the drug transporter is an opioid receptor antagonist.

178. The method of claim 172, wherein the opioid receptor antagonist is a compound selected from the group consisting of naltrexone, nalmefene and naloxone.

179. The method of claim 176, further comprising administering to the patient an opioid receptor agonist.

180. The method of claim 176, wherein the sub-therapeutic dose of the non-opioid CNS-active agent is less than the dose required to develop a drug dependence.

181. The method of claim 176, wherein the drug transporter is a P-glycoprotein.

182. The method of claim 181, wherein the P-glycoprotein is PGP1a.

183. The method of claim 179, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

184. The method of claim 183, wherein the adverse side effect is constipation.

185. The method of claim 176, wherein the inhibitor of the drug transporter is a compound listed in Table 11.

186. The method of claim 176, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

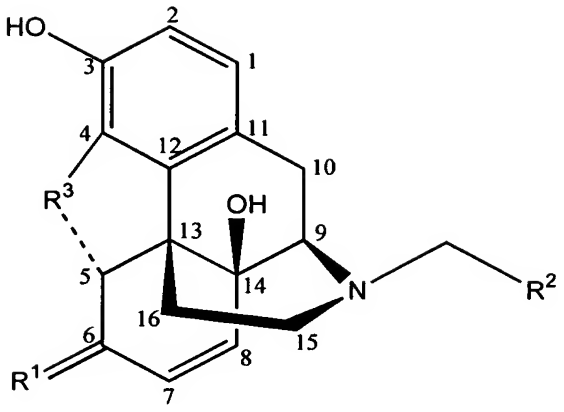
a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

187. A method of inhibiting a P-glycoprotein in a patient suffering from pain comprising administering to the patient a P-glycoprotein inhibiting amount of an inhibitor of an ABC drug transporter, wherein the inhibitor is selected from the group consisting of naltrexone, naloxone and nalmefene,

wherein the inhibitor is administered before, with, or after the administration to the patient of a therapeutically effective amount of a non-opioid CNS-active agent.

188. The method of claim 187, wherein the inhibitor is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

189. A method of enhancing efficacy of an opioid CNS-active agent comprising:

co-administering to a patient a therapeutic dose of the opioid CNS-active agent and an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the opioid CNS-active agent from the brain, wherein the drug transporter is an ABC drug transporter.

190. The method of claim 189, wherein the opioid CNS-active agent is an opioid receptor agonist.

191. The method of claim 190, wherein the opioid receptor is selected from the group consisting of morphine and oxycodone.

192. The method of claim 189, wherein the drug transporter is a P-glycoprotein.

193. The method of claim 192, wherein the P-glycoprotein is PGP1a.

194. The method of claim 189, further comprising administering to the patient an opioid receptor agonist.

195. The method of claim 190, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

196. The method of claim 195, wherein the adverse side effect is constipation.

197. The method of claim 189, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

198. The method of claim 189, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

199. A method of enhancing efficacy of an opioid CNS-active agent comprising:

co-administering to a patient a sub-therapeutic dose of the opioid CNS-active agent and an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the non-opioid CNS-active agent from the brain, wherein the drug transporter is an ABC drug transporter.

200. The method of claim 199, wherein the opioid CNS-active agent is an opioid receptor agonist.

201. The method of claim 200, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

202. The method of claim 199, wherein the drug transporter is a P-glycoprotein.

203. The method of claim 202, wherein the P-glycoprotein is PGP1a.

204. The method of claim 199, further comprising administering to the patient an opioid receptor agonist.

205. The method of claim 200, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

206. The method of claim 205, wherein the adverse side effect is constipation.

207. The method of claim 199, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

208. The method of claim 199, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

209. A method of enhancing efficacy of an opioid CNS-active agent comprising:

co-administering to a patient a therapeutic dose of the opioid CNS-active agent and an amount of a non-opioid inhibitor of a drug transporter effective to increase the concentration of the opioid CNS-active agent in the brain, wherein the drug transporter is an ABC drug transporter.

210. The method of claim 209, wherein the opioid CNS-active agent is an opioid receptor agonist.

211. The method of claim 210, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

212. The method of claim 209, wherein the drug transporter is a P-glycoprotein.

213. The method of claim 212, wherein the P-glycoprotein is PGP1a.

214. The method of claim 209, further comprising administering to the patient an opioid receptor agonist.

215. The method of claim 210, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

216. The method of claim 215, wherein the adverse side effect is constipation.

217. The method of claim 209, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

218. The method of claim 209, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

219. A method of enhancing efficacy of an opioid CNS-active agent comprising:

co-administering to a patient a sub-therapeutic dose of the opioid CNS-active agent and an amount of a non-opioid inhibitor of a drug transporter effective to increase the concentration of the opioid CNS-active agent in the brain, wherein the drug transporter is an ABC drug transporter.

220. The method of claim 219, wherein the opioid CNS-active agent is an opioid receptor agonist.

221. The method of claim ~~220,~~ wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

222 The method of claim 219, wherein the drug transporter is a P-glycoprotein.

223. The method of claim 222, wherein the P-glycoprotein is PGP1a.

224. The method of claim 219, further comprising administering to the patient an opioid receptor agonist.

225. The method of claim 220, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

226. The method of claim 225, wherein the adverse side effect is constipation.

227. The method of claim 219, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

228. The method of claim 219, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

229. A method of reversing tolerance to an opioid CNS-active agent comprising co-administering to a patient who is tolerant to the opioid CNS-active agent:

(a) an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the opioid receptor agonist from the brain, wherein the drug transporter is an ABC drug transporter, and

(b) the opioid CNS-active agent to which the patient developed tolerance.

230. The method of claim 229, wherein the opioid CNS-active agent is an opioid receptor agonist.

231. The method of claim 230, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

232. The method of claim 229, wherein the drug transporter is a P-glycoprotein.

233. The method of claim 232, wherein the P-glycoprotein is PGP1a.

234. The method of claim 229, further comprising administering to the patient an opioid receptor agonist.

235. The method of claim 230, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

236. The method of claim 235, wherein the adverse side effect is constipation.

237. The method of claim 229, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

238. The method of claim 229, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

239. A method of reversing tolerance to an opioid CNS-active agent comprising co-administering to a patient who is tolerant to the opioid CNS-active agent:

(a) an amount of a non-opioid inhibitor of a drug transporter effective to increase the concentration of the opioid receptor agonist in the brain, wherein the drug transporter is an ABC drug transporter, and

(b) the opioid CNS-active agent to which the patient developed tolerance.

240. The method of claim 239, wherein the opioid CNS-active agent is an opioid receptor agonist.

241. The method of claim 240, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

242. The method of claim 239, wherein the drug transporter is a P-glycoprotein.

243. The method of claim 242, wherein the P-glycoprotein is PGP1a.

244. The method of claim 239, further comprising administering to the patient an opioid receptor agonist.

245. The method of claim 240, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

246. The method of claim 245, wherein the adverse side effect is constipation.

247. The method of claim 239, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

248. The method of claim 239, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

249. A method of treating a patient with chronic pain comprising:

repeatedly over a period of time, co-administering to a patient a therapeutic or sub-therapeutic dose of an opioid CNS-active agent and an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the opioid CNS-active agent from the brain;

wherein the period of time is greater than the period of time in which the patient would develop tolerance to or develop dependence upon the opioid CNS-active agent administered in the absence of the non-opioid inhibitor of the drug transporter, and wherein the drug transporter is an ABC drug transporter.

250. The method of claim 249, wherein the period of time is greater than the period of time in which the patient would develop tolerance to the opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

251. The method of claim 249, wherein the period of time is greater than the period of time in which the patient would develop dependence upon the opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

252. The method of claim 249, further comprising administering to the patient an opioid receptor agonist.

253. The method of claim 249, wherein the opioid CNS-active agent is an opioid receptor agonist.

254. The method of claim 253, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

255. The method of claim 249, wherein the drug transporter is a P-glycoprotein.

256. The method of claim 255, wherein the P-glycoprotein is PGP1a.

257. The method of claim 250, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

258. The method of claim 257, wherein the adverse side effect is constipation.

259. The method of claim 249, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

260. The method of claim 249, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

261. A method of treating a patient with chronic pain comprising:

repeatedly over a period of time, co-administering to a patient a sub-analgesic dose of an opioid CNS-active agent and an amount of a non-opioid inhibitor of a drug transporter effective to increase the concentration of the opioid receptor agonist in the brain;

wherein the period of time is greater than the period of time in which the patient would develop tolerance to or develop dependence upon the opioid CNS-active agent administered in the absence of the non-opioid inhibitor of the drug transporter, and wherein the drug transporter is an ABC drug transporter.

262. The method of claim 261, wherein the period of time is greater than the period of time in which the patient would develop tolerance to the opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

263. The method of claim 261, wherein the period of time is greater than the period of time in which the patient would develop dependence upon the opioid CNS-active agent administered in the absence of the inhibitor of the drug transporter.

264. The method of claim 261, further comprising administering to the patient an opioid receptor agonist.

265. The method of claim 261, wherein the non-opioid CNS-active agent is an opioid receptor agonist.

266. The method of claim 265, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

267. The method of claim 261, wherein the drug transporter is a P-glycoprotein.

268. The method of claim 267, wherein the P-glycoprotein is PGP1a.

269. The method of claim 262, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

270. The method of claim 267, wherein the adverse side effect is constipation.

271. The method of claim 261, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

272. The method of claim 261, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

273. A method of controlling chronic pain without dependence comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of an opioid CNS-active agent; and

(b) an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the opioid CNS-active agent from the brain,

wherein the drug transporter is an ABC drug transporter , and wherein the co-administration of the non-opioid inhibitor of the drug transporter with the opioid CNS-active agent prevents the patient from developing dependence upon the opioid CNS-active agent.

274. The method of claim 273, wherein the sub-therapeutic dose of opioid CNS-active agent is less than the dose required to develop dependence upon the opioid CNS-active agent.

275. The method of claim 273, wherein the opioid CNS-active agent is an opioid receptor agonist.

276. The method of claim 275, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

277. The method of claim 273, wherein the drug transporter is a P-glycoprotein.

278. The method of claim 277, wherein the P-glycoprotein is PGP1a.

279. The method of claim 273, further comprising administering to the patient an opioid receptor agonist.

280. The method of claim 274, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

281. The method of claim 280, wherein the adverse side effect is constipation.

282. The method of claim 273, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

283. The method of claim 273, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

284. A method of controlling chronic pain without dependence comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of an opioid CNS-active agent; and

(b) an amount of a non-opioid inhibitor of a drug transporter effective to increase concentration of the opioid CNS-active agent in the brain,

wherein the drug transporter is an ABC drug transporter, and wherein the co-administration of the non-opioid inhibitor of the drug transporter with the opioid CNS-active agent prevents the patient from developing dependence upon the opioid CNS-active agent.

285. The method of claim 284, wherein the sub-therapeutic dose of the opioid CNS-active agent is less than the dose required to develop dependence upon the opioid CNS-active agent.

286. The method of claim 284, wherein the opioid CNS-active agent is an opioid receptor agonist.

287. The method of claim 286, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

288. The method of claim 284, wherein the drug transporter is a P-glycoprotein.

289. The method of claim 288, wherein the P-glycoprotein is PGP1a.

290. The method of claim 284, further comprising administering to the patient an opioid receptor agonist.

291. The method of claim 285, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

292. The method of claim 291, wherein the adverse side effect is constipation.

293. The method of claim 284, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

294. The method of claim 284, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

295. A method of controlling chronic pain without tolerance comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of an opioid CNS-active agent; and

(b) an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the opioid CNS-active agent from the brain,

wherein the drug transporter is an ABC drug transporter, and wherein the co-administration of the non-opioid inhibitor of the drug transporter with the opioid CNS-active agent prevents the patient from developing tolerance to the opioid CNS-active agent.

296. The method of claim 295, wherein the sub-therapeutic dose of the opioid CNS-active agent is less than the dose required to develop tolerance to the opioid CNS-active agent.

297. The method of claim 295, wherein the opioid CNS-active agent is an opioid receptor agonist.

298. The method of claim 297, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

299. The method of claim 295, wherein the drug transporter is a P-glycoprotein.

300. The method of claim 299, wherein the P-glycoprotein is PGP1a.

301. The method of claim 295, further comprising administering to the patient an opioid receptor agonist.

302. The method of claim 296, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

303. The method of claim 302, wherein the adverse side effect is constipation.

304. The method of claim 295, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

305. The method of claim 295, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

306. A method of controlling chronic pain without tolerance comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of an opioid CNS-active agent; and

(b) an amount of a non-opioid inhibitor of a drug transporter effective to increase concentration of the opioid CNS-active agent in the brain,

wherein the drug transporter is an ABC drug transporter, and wherein the co-administration of the non-opioid inhibitor of the drug transporter with the opioid CNS-active agent prevents the patient from developing tolerance to the opioid CNS-active agent.

307. The method of claim 306, wherein the sub-therapeutic dose of the opioid CNS-active agent is less than the dose required to develop tolerance to the opioid CNS-active agent.

308. The method of claim 306, wherein the opioid CNS-active agent is an opioid receptor agonist.

309. The method of claim 308, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

310. The method of claim 306, wherein the drug transporter is a P-glycoprotein.

311. The method of claim 310, wherein the P-glycoprotein is PGP1a.

312. The method of claim 306, further comprising administering to the patient an opioid receptor agonist.

313. The method of claim 307, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

314. The method of claim 313, wherein the adverse side effect is constipation.

315. The method of claim 306, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

316. The method of claim 306, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

317. A method of controlling chronic pain without withdrawal comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of an opioid CNS-active agent; and

(b) an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the opioid CNS-active agent from the brain,

wherein the drug transporter is an ABC drug transporter, and wherein the co-administration of the non-opioid inhibitor of the drug transporter with the opioid CNS-active agent prevents the patient from developing withdrawal.

318. The method of claim 317, wherein the sub-therapeutic dose of the opioid CNS-active agent is less than the dose required to develop withdrawal.

319. The method of claim 317, wherein the opioid CNS-active agent is an opioid receptor agonist.

320. The method of claim 319, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

321. The method of claim 317, wherein the drug transporter is a P-glycoprotein.

322. The method of claim 321, wherein the P-glycoprotein is PGP1a.

323. The method of claim 317, further comprising administering to the patient an opioid receptor agonist.

324. The method of claim 318, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

325. The method of claim 324, wherein the adverse side effect is constipation.

326. The method of claim 317, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

327. The method of claim 317, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

328. A method of controlling chronic pain without withdrawal comprising co-administering to a patient:

(a) a therapeutic or sub-therapeutic dose of an opioid CNS-active agent; and

(b) an amount of a non-opioid inhibitor of a drug transporter effective to increase concentration of the opioid CNS-active agent in the brain,

wherein the drug transporter is an ABC drug transporter, and wherein the co-administration of the non-opioid inhibitor of the drug transporter with the opioid CNS-active agent prevents the patient from developing withdrawal.

329. The method of claim 328, wherein the sub-therapeutic dose of the opioid CNS-active agent is less than the dose required to develop withdrawal.

330. The method of claim 328, wherein the opioid CNS-active agent is an opioid receptor agonist.

331. The method of claim 330, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

332. The method of claim 328, wherein the drug transporter is a P-glycoprotein.

333. The method of claim 332, wherein the P-glycoprotein is PGP1a.

334. The method of claim 328, further comprising administering to the patient an opioid receptor agonist.

335. The method of claim 329, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

336. The method of claim 335, wherein the adverse side effect is constipation.

337. The method of claim 328, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

338. The method of claim 328, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

339. A method of preventing a patient from becoming tolerant to or dependent upon an opioid CNS-active agent comprising co-administering to the patient:

(a) an amount of a non-opioid inhibitor of a drug transporter effective to reduce efflux of the opioid CNS-active agent from the brain, wherein the drug transporter is an ABC drug transporter; and

(b) a therapeutic or sub-therapeutic dose of the opioid CNS-active agent, thereby preventing the patient from becoming tolerant to or dependent upon the opioid CNS-active agent.

340. The method of 339, wherein the sub-therapeutic dose of the opioid CNS-active agent is less than the dose required to develop tolerance to or dependence upon the opioid CNS-active agent.

341. The method of claim 339, wherein the opioid CNS-active agent is an opioid receptor agonist.

342. The method of claim 341, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

343. The method of claim 339, wherein the drug transporter is a P-glycoprotein.

344. The method of claim 343, wherein the P-glycoprotein is PGP1a.

345. The method of claim 339, further comprising administering to the patient an opioid receptor agonist.

346. The method of claim 340, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

347. The method of claim 346, wherein the adverse side effect is constipation.

348. The method of claim 339, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

349. The method of claim 339, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

350. A method of preventing a patient from becoming tolerant to or dependent upon an opioid CNS-active agent comprising co-administering to the patient:

(a) an amount of a non-opioid inhibitor of a drug transporter effective to increase the concentration of the opioid CNS-active agent in the brain, wherein the drug transporter is an ABC drug transporter; and

(b) administering to the patient a therapeutic or sub-therapeutic dose of the opioid CNS-active agent, thereby preventing the patient from becoming tolerant to or dependent upon the opioid CNS-active agent.

351. The method of claim 350, wherein the sub-therapeutic dose of the opioid CNS-active agent is less than the dose required to develop tolerance to or dependence upon the CNS-active agent.

352. The method of claim 350, wherein the opioid CNS-active agent is an opioid receptor agonist.

353. The method of claim 352, wherein the opioid receptor agonist is selected from the group consisting of morphine and oxycodone.

354. The method of claim 350, wherein the drug transporter is a P-glycoprotein.

355. The method of claim 354, wherein the P-glycoprotein is PGP1a.

356 The method of claim 350, further comprising administering to the patient an opioid receptor agonist.

357. The method of claim 351, wherein an adverse side effect associated with the administration of the opioid receptor agonist is attenuated by the non-opioid inhibitor of the drug transporter.

358. The method of claim 357, wherein the adverse side effect is constipation.

359. The method of claim 350, wherein the non-opioid inhibitor of the drug transporter is a compound listed in Table 11.

360. The method of claim 350, wherein the inhibitor of the drug transporter is a compound having the pharmacophore defined by:

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 3 of naltrexone;

a hydrogen bonding moiety at a three-dimensional location corresponding to the hydroxyl at position 14 of naltrexone;

a hydrophobic moiety at a three-dimensional location corresponding to the cyclopropyl moiety appended to the nitrogen of naltrexone; and

a region of electron density at a three-dimensional location corresponding to the ethylene moiety at 6-position of naltrexone.

361. A composition comprising:

(a) an opioid receptor agonist; and

(b) a non-opioid compound

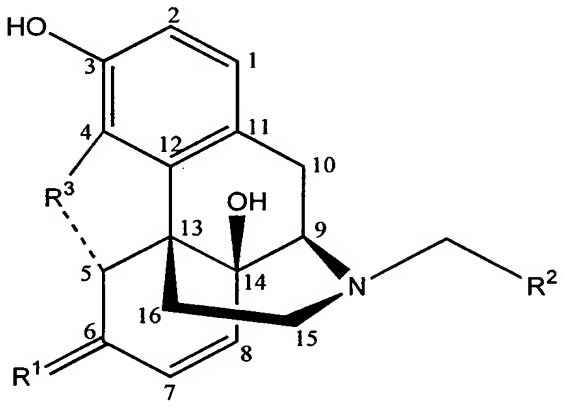
wherein the non-opioid compound is capable of inhibiting a drug transporter, wherein the drug transporter is an ABC drug transporter.

362. A composition comprising

(a) a non-opioid CNS-active agent; and

(b) an opioid receptor antagonist.

363. The composition of claim 362, wherein the opioid receptor antagonist is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

364. A composition comprising

(a) a non-opioid CNS-active agent; and

(b) an opioid inhibitor of an ABC drug transporter.

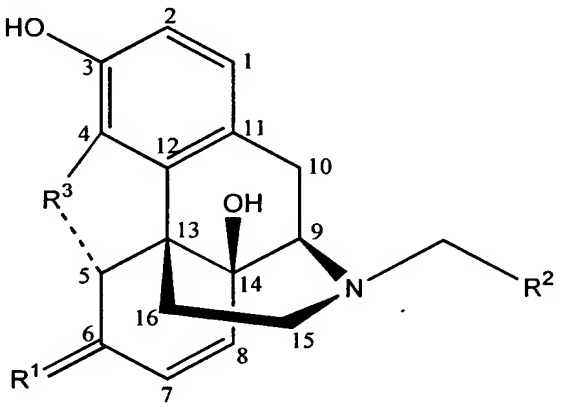
365. The composition of claim 364, wherein the ABC drug transporter is a PGP drug transporter.

366. The composition of claim 365, wherein the PGP drug transporter is a PGP1a drug transporter.

367. The composition of claim 364, wherein the opioid inhibitor is an opioid receptor antagonist.

368. The composition of claim 367, wherein the opioid receptor antagonist is selected from the group consisting of naltrexone, naloxone, and nalmefene.

369. The composition of claim 364, wherein the inhibitor is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

370. A composition comprising

(a) an opioid CNS-active agent; and

(b) a non-opioid inhibitor of an ABC drug transporter.

371. The composition of claim 370, wherein the ABC drug transporter is a PGP drug transporter.

372. The composition of claim 371, wherein the PGP drug transporter is a PGP1a drug transporter.

373. A composition comprising:

(a) a non-opioid CNS-active agent, and

(b) an opioid receptor antagonist that is an inhibitor of an ABC drug transporter,

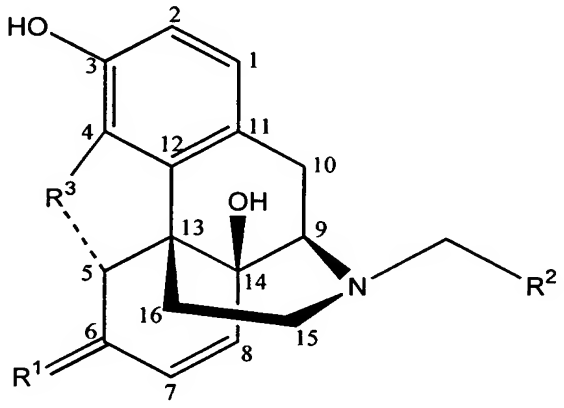
wherein the composition is for the treatment of chronic pain, for controlling pain without dependence, tolerance, or withdrawal, or

.

374. The composition of claim 373, wherein the opioid receptor antagonist is selected from the group consisting of naltrexone, naloxone, and nalmefene.

375. The composition of claim 373, wherein the non-opioid CNS-active agent is selected from the group consisting of valium, lithium, halcyon, and ambien.

376. The composition of claim 373, wherein the opioid receptor antagonist is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

377. A method of identifying a compound suitable for co-administration with a CNS-active agent for enhanced efficacy of the CNS-active agent, the method comprising:

(a) assaying a test compound for inhibition of an ABC drug transporter by

(i) applying a known inhibitor of the ABC drug transporter to an ABC drug transporter barrier in the in the presence and absence of the test compound, and

(ii) comparing the concentration of the known inhibitor that has been transported across the ABC drug transporter in the presence of the test compound with the concentration of the known inhibitor that has been transported across the ABC drug transporter barrier in the absence of the test compound, and

(b) selecting the test compound if the concentration of the known inhibitor that has been transported across the ABC drug transporter in the presence of the test compound is decreased relative to the concentration of the known inhibitor that has been transported across the ABC drug transporter barrier in the absence of the test compound,

wherein the known inhibitor is selected from the group consisting of naltrexone, nalmefene and naloxone.

378. The method of claim 377, wherein the step of assaying a test compound comprises screening a library of test compounds.

379. The method of claim 377, wherein the ABC drug transporter is a P-glycoprotein.

380. The method of claim 379, wherein the P-glycoprotein is PGP1a.

381. The method of claim 377, wherein the CNS-active agent is a non-opioid.

382. The method of claim 381, wherein the selected test compound is opioid.

383. The method of claim 377, wherein the CNS-active agent is an opioid and the selected test compound is a non-opioid.

384. A method of identifying a compound suitable for co-administration with a CNS-active agent for enhanced efficacy of the CNS-active agent, the method comprising:

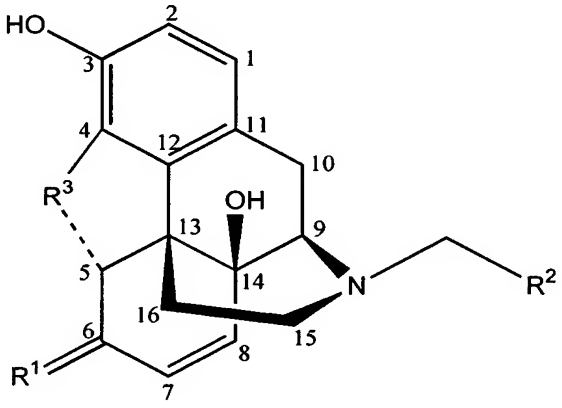
(a) assaying a test compound for inhibition of an ABC drug transporter by

(i) applying a known inhibitor of the ABC drug transporter to an ABC drug transporter barrier in the in the presence and absence of the test compound, and

(ii) comparing the concentration of the known inhibitor that has been transported across the ABC drug transporter in the presence of the test compound with the concentration of the known inhibitor that has been transported across the ABC drug transporter barrier in the absence of the test compound, and

(b) selecting the test compound if the concentration of the known inhibitor that has been transported across the ABC drug transporter in the presence of the test compound is decreased relative to the concentration of the known inhibitor that has been transported across the ABC drug transporter barrier in the absence of the test compound,

wherein the known inhibitor is a compound of the formula:



wherein R^1 is CH_2 or O;

wherein R^2 is a cycloalkyl, unsubstituted aromatic, alkyl or alkenyl; and

wherein R^3 is O, CH_2 or NH.

385. The method of claim 384, wherein the step of assaying a test compound comprises screening a library of test compounds.

386. The method of claim 384, wherein the ABC drug transporter is a P-glycoprotein.

387. The method of claim 386, wherein the P-glycoprotein is PGP1a.

388. The method of claim 384, wherein the CNS-active agent is a non-opioid.

389. The method of claim 388, wherein the selected test compound is opioid.

390. The method of claim 384, wherein the CNS-active agent is an opioid and the selected test compound is a non-opioid.

391. A method of identifying a compound as a therapeutic agent for transport across the blood brain barrier comprising:

(a) identifying a therapeutic agent which is active in the brain;

(b) assaying the ability of the therapeutic agent to be transported across a membrane by an ABC drug transporter; and

(c) repeating the transport assay to determine whether addition of an opioid receptor antagonist inhibits transport of the therapeutic agent across the membrane,

whereby the compound which is active in the brain, is transported by an ABC protein and whose ABC protein-mediated transport is inhibited by the opioid receptor antagonist is identified as a compound for transport across the blood brain barrier.

392. The method of claim 391, wherein the opioid receptor antagonist is nalmefene, naloxone, or naltrexone.

393. A method of enhancing the potency of a compound identified by the method of claim 391 comprising:

co-administering a therapeutic amount of the compound and an amount of an opioid receptor antagonist capable of inhibiting a drug transporter, wherein the amount of the opioid receptor antagonist is sufficient to reduce transport of the compound across a biological membrane.